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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,458	08/13/2001	David Wallach	WALLACH=22A	6865

7590 07/16/2002

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	7

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,458	WALLACH ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-24,27 and 28* is/are pending in the application.

4a) Of the above claim(s) *17-24,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13, 15 and 16* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/13/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 13-24 and 27-28 are pending.

2. Applicant's election with traverse of Group III, Claims 13-16 drawn to a polypeptide capable of binding to RIP, filed 5/6/02, is acknowledged. The traversal is on the grounds that the antibody (Group IV) and polypeptide (Group III) are not distinct, if the antibody of claim 13 were available to the to the prior art which includes knowledge of its biological activity as set forth in the claim, it would be prima facie obvious for one of ordinary skill in the art to make an antibody. This is not found persuasive because of the reasons set forth in the restriction mailed 5/6/02. Inventions of Groups III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the antibody and polypeptide as claimed differ with respect to their structure and physiochemical properties. Therefore, they are patentably distinct. Further, Applicant may file a divisional application for the antibody and still gets the effect filing date of the parent application. Finally, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group III and Groups I-II and IV-VII is still deemed proper and is therefore made FINAL.

3. Claims 17-24 and 27-28 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 13-16 are being acted upon in this Office Action.

5. The references cited on PTO 1449 filed 8/13/01 have been crossed out because none of the cited references have been submitted to the Office.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 13 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide comprising SEQ ID NO: 2 which is capable of binding to receptor interacting protein (RIP) and inhibits the Jun kinase induction in vitro or a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which is capable of binding to receptor interacting protein (RIP) and inhibits the Jun kinase induction in vitro, **does not** reasonably provide enablement for (1) *any* fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which is capable of binding to RIP or inhibiting the NF-kB inducing effect of RIP, (2) *any* analog of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which differs from said sequence by no more than 10 substitutions, deletions and/or insertions of amino acid residues and is capable of binding to RIP or inhibiting the NFkB inducing effect of RIP, (3) *any* analog of *any* fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which differs from the sequence of the fragment mentioned above by no more than 10 substitutions, deletions and/or insertions of amino acid residues and is capable of binding to RIP or inhibiting the NFkB inducing effect of RIP, (4) *any* polypeptide mentioned above which "has" the amino acid sequence of a fragment of a RIP associated protein (RAP) encoded by a DNA sequence under the accession number I-2706, and (5) *any* pharmaceutical composition for the modulation of the RIP effect on cells, comprising as active ingredient, *any* polypeptide, fragment, analog mentioned above for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one polypeptide comprising the amino acid sequence of SEQ ID NO: 2 potentially encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 for blocking Jun kinase induction caused by RIP (See page 86 of the specification). The specification on page 86, line 5-7 discloses that RAP **was incapable** of binding to any of the known intracellular signaling proteins such as MORT-1/FADD, TRAF1, TRAF2, MACH, Mch34, and G1 mentioned above, including the irrelevant control proteins, such as lamin and cyclin D. The specification further discloses the following biological activities (i) RAP is not toxic to cells on its own when overexpressed, (ii) RAP does not protect cells from TNF killing, (iii) RAP does not induce NF-κB on its own, (iv) RAP does block NF-κB activation by TRADD, RIP and p55 TNF-R and (v) blocks Jun kinase induction caused by RIP (See page 87 of the specification).

Other than the specific polypeptide mentioned above for blocking Jun kinase induction caused by RIP and NF-κB activation by TRADD, RIP and p55 TNF-R in vitro, the specification does not teach how to make and use *any* fragment, *any* analog, *any* analog of *any* undisclosed fragment because there is no structure associated with the term "fragment" and "analog" such as the specific amino acid residues that makes up the fragment or analog. Given the indefinite number of undisclosed fragment and analog, it is unpredictable which undisclosed fragment, analog, and fragment of an undisclosed analog would have the same structure and function as the claimed polypeptide of SEQ ID NO: 2 which encoded by a DNA sequence in a clone deposited under the accession number I-2706. Further, the term "has" is open ended. It expands the fragment of a RIP associated protein (RAP) encoded by a DNA sequence under the accession number I-2706 to include additional amino acids at either or both ends. There is insufficient guidance and working example in the specification as to what type and number of amino acids within the amino acid sequence (polypeptide) of SEQ ID NO: 2 can be deleted and whether after deletion would retain both structure and function of polypeptide of SEQ ID NO: 2, which is encoded by a DNA sequence in a clone deposited under the accession number I-2706.

With regard to "analog" of *any* isolated polypeptide mentioned above which differs from the claimed sequence or fragment of the claimed sequence by no more than 10 substitution, deletion, and/or insertions, there is no guidance and working examples in the specification as filed as to which specific amino acid within the full length polypeptide of SEQ ID NO: 2 that has 522

amino acids in length or any fragment thereof can be substitute, delete, and/or added and that after modification will maintain both structure and functional biological activity such as inhibiting Jun kinase induction or blocking NF-kappaB activation by TRADD, RIP and p55 TNF-R pathways.

Lin *et al* teach a variety of signals induce activation of NF-kappaB (See page 5899, column 1, first full paragraph, in particular) and RIP plays a structural rather than an enzymatic role in the TNFα response (See page 5899, column 2, last paragraph, in particular).

Kim *et at* teach a single amino acid change from D to A at position 324 of RIP (RIPD324A) activates NF-kappaB activation while ectopic expression of proapoptotic C-terminal fragment of RIP inhibited TNF-induced NF-kappaB activation (Abstract, in particular). The specification discloses only **one** polypeptide of SEQ ID NO: 2. There are no additional polypeptide, fragment and analog thereof which have been demonstrate to be useful for modulating such as inhibiting or enhancing the intracellular effect of *any* RIP. Given the lack of guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 2, which encoded by that after substitution, deletion, insertion and/or modification will retain both structure and have similar function is unpredictable.

Regarding "pharmaceutical composition" for "modulating" a*ny* "RIP" effect comprising *any* fragment, *any* analog, and *any* analog of *any* fragment of RIP-associated protein mentioned above, there are no in vivo working examples in the specification to demonstrate that any fragment, and analog mentioned above have *any* in vivo activity. A "pharmaceutical composition" in the absence of in vivo data are unpredictable for the following reasons; (1) the polypeptide, fragment and/or analog thereof may be inactivated before producing an effect, i.e. such as proteolytic degradation; (2) the polypeptide, fragment and/or analog thereof may not reach the target area because, i.e. the polypeptide may target to elsewhere for degradation, or has no effect; and (3) other functional properties, known or unknown, may make the polypeptide, fragment and/or analog thereof unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Since *any* amino acid sequence that comprises "a fragment" of SEQ ID NO: 2, an analog of a RIP-associated protein (RAP) and an analog of a fragment of a RIP-associated protein are not adequately described, it follows that a pharmaceutical composition comprising said fragment, analog, and analog of a fragment of a RIP-associated protein is not enable.

For these reasons, the specification as filed fails to enable even one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

8. Claims 13 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which is capable of binding to RIP or inhibiting the NF-kB inducing effect of RIP, (2) *any* analog of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which differs from said sequence by no more than 10 substitutions, deletions and/or insertions of amino acid residues and is capable of binding to RIP or inhibiting the NFkB inducing effect of RIP, (3) *any* analog of *any* fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which differs from the sequence of the fragment mentioned above by no more than 10 substitutions, deletions and/or insertions of amino acid residues and is capable of binding to RIP or inhibiting the NFkB inducing effect of RIP, (4) *any* polypeptide mentioned above which "has" the amino acid sequence of a fragment of a RIP associated protein (RAP) encoded by a DNA sequence under the accession number I-2706, and (5) *any* pharmaceutical composition for the modulation of the RIP effect on cells, comprising as active ingredient, *any* polypeptide, fragment, analog mentioned above for treating *any* disease.

The specification discloses only one polypeptide comprising the amino acid sequence of SEQ ID NO: 2 potentially encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 for blocking Jun kinase induction caused by RIP (See page 86 of the specification). The specification on page 86, line 5-7 discloses that RAP **was incapable** of binding to any of the known intracellular signaling proteins such as MORT-1/FADD, TRAF1, TRAF2, MACH, Mch34, and G1 mentioned above, including the irrelevant control proteins, such as lamin and cyclin D. The specification further

discloses the following biological activities (i) RAP is not toxic to cells on its own when overexpressed, (ii) RAP does not protect cells from TNF killing, (iii) RAP does not induce NF-κB on its own, (iv) RAP does block NF-κB activation by TRADD, RIP and p55 TNF-R and (v) blocks Jun kinase induction caused by RIP (See page 87 of the specification).

Other than the specific polypeptide mentioned above for blocking Jun kinase induction and blocking NF-κB activation by TRADD, RIP and p55 TNF-R *in vitro*, there is insufficient written description about the structure associated with functions of *any* "fragment", *any* "analog" and *any* analog of any fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited under the accession number I-2706. Further, the term "has" is open ended. It expands the fragment of a RIP associated protein (RAP) encoded by a DNA sequence under the accession number I-2706 to include additional amino acids at either or both ends.

Since *any* amino acid sequence that comprises "a fragment" of SEQ ID NO: 2, an analog of a RIP-associated protein (RAP) and an analog of a fragment of a RIP-associated protein are not adequately described, it follows that a pharmaceutical composition comprising said fragment, analog, and analog of a fragment of a RIP-associated protein is not adequately described. Given the lack of a written description of *any* additional representative species of polypeptide, fragment and analog thereof as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

10. Claims 13, 15 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,232,081 (May 2001, PTO 892).

The '081 patent teaches an isolated polypeptide which has the amino acid sequence such as LPLELKLRIFRLLDVRSVLSLSAVCRDLFTASNDPLLW, which is a fragment of the claimed polypeptide of SEQ ID NO: 2 encoding by a DNA clone under the accession number I-2706 (See SEQ ID NO: 47 of '081, column 2, lines 30-32, in particular). The functional properties of the reference fragment such as capable of inhibiting the NF-κB inducing effect of RIP or induction of NF-κB activity protects cell against TNF-mediated cell death is an inherent properties of the reference fragment because the claimed fragment of RIP appears to be the same as the reference fragment (See entire document, column 41, lines 44-45, in particular). The '081 patent teaches compositions comprising the reference protein and methods for development of drugs that disrupt at least one pathway in which the reference proteins function to ameliorate the effects of inflammatory response (See column 4, lines 37-50, in particular). Thus, the reference teachings anticipate the claimed invention.

11. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
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July 15, 2002

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